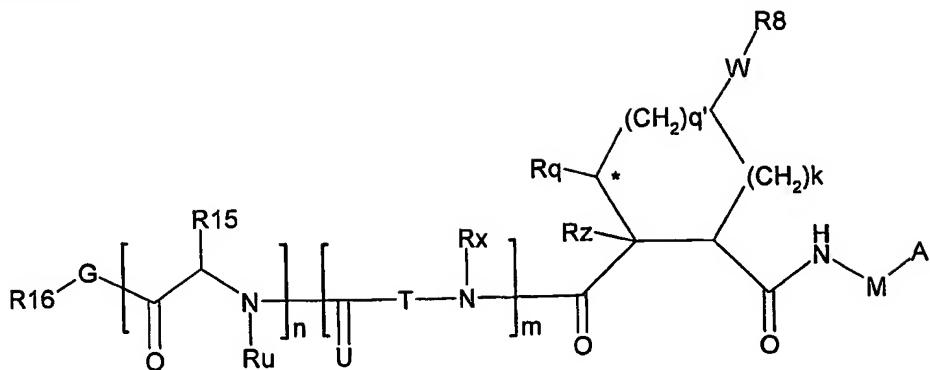


Claims

1. A compound of the formula VI:



5 wherein

A is $\text{C}(=\text{O})\text{OR}^1$, $\text{C}(=\text{O})\text{NHSO}_2\text{R}^2$, $\text{C}(=\text{O})\text{NHR}^3$, or $\text{CR}^4\text{R}^4'$ wherein;

R^1 is hydrogen, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_0\text{-C}_3$ alkylcarbocyclyl, $\text{C}_0\text{-C}_3$ alkylheterocyclyl;

R^2 is $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_0\text{-C}_3$ alkylcarbocyclyl, $\text{C}_0\text{-C}_3$ alkylheterocyclyl;

R^3 is $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_0\text{-C}_3$ alkylcarbocyclyl, $\text{C}_0\text{-C}_3$ alkylheterocyclyl, $-\text{OC}_1\text{-C}_6$ alkyl, $-\text{OC}_0\text{-}$

10 C_3 alkylcarbocyclyl, $-\text{OC}_0\text{-C}_3$ alkylheterocyclyl;

R^4 is halo, amino, or OH; or R^4 and R^4' together are =O;

R^4' is $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_0\text{-C}_3$ alkylcarbocyclyl, $\text{C}_0\text{-C}_3$ alkylheterocyclyl;

wherein R^2 , R^3 , and R^4 are each optionally substituted from 1 to 3 substituents independently selected from the group consisting of halo, oxo, nitrile, azido, nitro, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_0\text{-C}_3$ alkylcarbocyclyl, $\text{C}_0\text{-C}_3$ alkylheterocyclyl, $\text{NH}_2\text{C}(=\text{O})-$, Y-NRaRb , Y-O-

15 R_b , $\text{Y-C}(=\text{O})\text{Rb}$, Y-(C=O)NRaRb , $\text{Y-NRaC}(=\text{O})\text{Rb}$, $\text{Y-NHSO}_p\text{Rb}$, $\text{Y-S}(=\text{O})_p\text{Rb}$, Y-

$\text{S}(=\text{O})_p\text{NRaRb}$, $\text{Y-C}(=\text{O})\text{Orb}$ and $\text{Y-NRaC}(=\text{O})\text{ORb}$;

Y is independently a bond or $\text{C}_1\text{-C}_3$ alkylene;

Ra is independently H or $\text{C}_1\text{-C}_3$ alkyl;

20 Rb is independently H, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_0\text{-C}_3$ alkylcarbocyclyl or $\text{C}_0\text{-C}_3$ alkylheterocyclyl;

p is independently 1 or 2;

M is $\text{CR}^7\text{R}^7'$ or NRu ;

Ru is H or $\text{C}_1\text{-C}_3$ alkyl;

R⁷ is C₁-C₆alkyl, C₀-C₃alkylC₃-C₇cycloalkyl, or C₂-C₆alkenyl, any of which is optionally substituted with 1-3 halo atoms, or an amino, -SH or C₀-C₃alkylcycloalkyl group; or R⁷ is J;

R⁷ is H or taken together with R⁷ forms a C₃-C₆cycloalkyl ring optionally substituted with R^{7'a} wherein;

R^{7'a} is C₁-C₆alkyl, C₃-C₅cycloalkyl, C₂-C₆alkenyl any of which may be optionally substituted with halo; or R^{7'a} is J;

q' is 0 or 1 and k is 0 to 3;

Rz is H, or together with the asterisked carbon forms an olefinic bond;

10 Rq is H or C₁-C₆alkyl;

W is -CH₂-, -O-, -OC(=O)H-, -OC(=O)-, -S-, -NH-, -NRa, -NHSO₂-, -NHC(=O)NH- or -NHC(=O)-, -NHC(=S)NH- or a bond;

R⁸ is a ring system containing 1 or 2 saturated, partially saturated or unsaturated rings each of which has 4-7 ring atoms and each of which has 0 to 4 hetero atoms

15 selected from S, O and N, the ring system being optionally spaced from W by a C₁-C₃alkyl group; or R⁸ is C₁-C₆alkyl; any of which R⁸ groups can be optionally mono, di, or tri substituted with R⁹, wherein

R⁹ is independently selected from the group consisting of halo, oxo, nitrile, azido, nitro, C₁-C₆alkyl, C₀-C₃alkylcarbocyclyl, C₀-C₃alkylheterocyclyl, NH₂C(=O)-, Y-

20 NRaRb, Y-O-Rb, Y-C(=O)Rb, Y-(C=O)NRaRb, Y-NRaC(=O)Rb, Y-NHSO_pRb, Y-S(=O)_pRb, Y-S(=O)_pNRaRb, Y-C(=O)ORb and Y-NRaC(=O)ORb; wherein said carbocyclyl or heterocyclyl moiety is optionally substituted with R¹⁰; wherein

R¹⁰ is C₁-C₆alkyl, C₃-C₇cycloalkyl, C₁-C₆alkoxy, amino, sulfonyl, (C₁-C₃ alkyl)sulfonyl, NO₂, OH, SH, halo, haloalkyl, carboxyl, amido;

25 Rx is H or C₁-C₅ alkyl; or Rx is J;

T is -CHR¹¹- or -NRd-, where Rd is H, C₁-C₃alkyl or Rd is J;

R¹¹ is H or R¹¹ is C₁-C₆alkyl, C₀-C₃alkylcarbocyclyl, C₀-C₃alkylheterocyclyl, any of which can be substituted with 1 to 3 substituents independently selected from the group consisting of halo, oxo, nitrile, azido, nitro, C₁-C₆alkyl, C₀-C₃alkylcarbocyclyl, C₀-C₃alkylheterocyclyl, NH₂CO-, Y-NRaRb, Y-O-Rb, Y-C(=O)Rb, Y-(C=O)NRaRb, Y-

NR_aC(=O)R_b, Y-NHSO_pR_b, Y-S(=O)_pR_b, Y-S(=O)_pNR_aR_b, Y-C(=O)OR_b, Y-NR_aC(=O)OR_b; or R¹¹ is J;

J, if present, is a single 3 to 10-membered saturated or partially unsaturated alkylene chain extending from the R⁷/R⁷' cycloalkyl, or from the carbon atom to which R⁷ is

5 attached to one of R_d, R_j, R_x, R_y or R¹¹ to form a macrocycle, which chain is optionally interrupted by one to three heteroatoms independently selected from: -O-, -S- or -NR¹²-, and wherein 0 to 3 carbon atoms in the chain are optionally substituted with R¹⁴; wherein;

R¹² is H, C₁-C₆ alkyl, C₃-C₆cycloalkyl, or COR¹³,

10 R¹³ is C₁-C₆alkyl, C₀-C₃alkylcarbocyclyl, C₀-C₃alkylheterocyclyl;

R¹⁴ is independently selected from H, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆alkoxy, hydroxy, halo, amino, oxo, thio, or C₁-C₆ thioalkyl;

m is 0 or 1; n is 0 or 1;

U is O or is absent;

15 R¹⁵ is H, C₁-C₆alkyl, C₀-C₃alkylcarbocyclyl, C₀-C₃alkylheterocyclyl, any of which can be substituted with 1 to 3 substituents independently selected from the group consisting of halo, oxo, nitrile, azido, nitro, C₁-C₆ alkyl, C₀-C₃alkylheterocyclyl, C₀-C₃alkylcarbocyclyl, NH₂C(=O)-, Y-NR_aR_b, Y-O-R_b, Y-C(=O)R_b, Y-(C=O)NR_aR_b, Y-NR_aC(=O)R_b, Y-NHSO_pR_b, Y-S(=O)_pR_b, Y-S(=O)_pNR_aR_b, Y-C(=O)OR_b and Y-

20 NR_aC(=O)OR_b;

G is -O-, -NR_y-, -NR_jNR_j-;

Ry is H, C₁-C₃ alkyl; or Ry is J;

one R_j is H and the other R_j is H or J;

R¹⁶ is H; or R¹⁶ is C₁-C₆alkyl, C₀-C₃alkylcarbocyclyl, C₀-C₃alkylheterocyclyl, any of

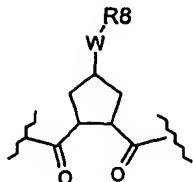
25 which can be substituted with halo, oxo, nitrile, azido, nitro, C₁-C₆alkyl, C₀-C₃alkylcarbocyclyl, C₀-C₃alkylheterocyclyl, NH₂CO-, Y-NR_aR_b, Y-O-R_b, Y-C(=O)R_b, Y-(C=O)NR_aR_b, Y-NR_aC(=O)R_b, Y-NHSO_pR_b, Y-S(=O)_pR_b, Y-S(=O)_pNR_aR_b, Y-C(=O)OR_b, Y-NR_aC(=O)OR_b;

or a pharmaceutically acceptable salt or prodrug thereof.

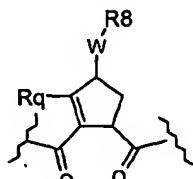
30

2. A compound according to claim 1, where M is CR⁷R⁷'.

3. A compound according to claim 1, with the partial structure:



4. A compound according to claim 1, with the partial structure



5 5. A compound according to claim 4, wherein Rq is C₁-C₃ alkyl, preferably methyl.

6 6. A compound according to claim 1, wherein m is 0 and n is 0.

10 7. A compound according to claim 6, wherein G is -NRy- or -NRjNRj-.

8 8. A compound according to claim 7, where Ry or one of the Rj groups is J, thereby defining a macrocyclic compound.

15 9. A compound according to claim 7, wherein R¹⁶ is H, C₁-C₆alkyl or C₃-C₆ cycloalkyl.

10 10. A compound according to claim 1, wherein m is 1.

20 11. A compound according to claim 10, wherein U is O.

12. A compound according to claim 10, wherein T is CR¹¹.

25 13. A compound according to claim 12, wherein R¹¹ is C₁-C₆alkyl, C₀-C₃alkylcarbocyclyl, C₀-C₃alkylaryl or C₀-C₃alkylheteroaryl, any of which is optionally

substituted with halo, amino, C₁-C₆alkoxy, C₁-C₆thioalkyl, COOR¹⁴, carboxyl, (C₁-C₆alkoxy)carbonyl, aryl, heteroaryl or heterocycl; or especially substituted with hydroxyl or COOR¹⁴.

5 14. A compound according to claim 13, wherein R¹¹ is tert-butyl, iso-butyl, cyclohexyl, phenylethyl, 2,2-dimethyl-propyl, cyclohexylmethyl, phenylmethyl, 2-pyridylmethyl, 4-hydroxy-phenylmethyl, or carboxylpropyl, especially tert-butyl, iso-butyl, or cyclohexyl.

10 15. A compound according to claim 10, wherein one of Rd, Rx or R¹¹ is J, thereby defining a macrocyclic compound.

16. A compound according to claim 10, wherein n is 1.

15 17. A compound according to claim 16, wherein R¹⁵ is C₁-C₆alkyl or C₀-C₃alkylcarbocycl, either of which is optionally substituted.

18. A compound according to claim 17, wherein R¹⁵ is cyclohexyl, cyclohexylmethyl, tert-butyl, iso-propyl, or iso-butyl.

20 19. A compound according to claim 10, wherein G is NRy or NRjNRj, where Ry or one Rj is H or methyl and the other is H.

25 20. A compound according to claim 19, wherein R¹⁶ is H, C₁-C₆alkyl or a 5 or 6 membered heterocycle, especially morpholine, piperidine or piperazine.

21. A compound according to claim 10, wherein R¹⁶ is C₁-C₆alkyl, C₀-C₃alkylheterocycl, C₀-C₃alkylcarbocycl, any of which is optionally substituted with hydroxy, halo, amino, or C₁-C₆alkoxy.

22. A compound according to claim 21, wherein R¹⁶ is 2-indanol, indanyl, 2-hydroxy-1-phenyl-ethyl, 2-thiophenemethyl, cyclohexylmethyl, 2,3-methylenedioxybenzyl, cyclohexyl, benzyl, 2-pyridylmethyl, cyclobutyl, iso-butyl, n-propyl, or 4-methoxyphenylethyl.

5

23. A compound according to claim 1, wherein W is -OC(=O)-, -NRa-, -NHS(O)₂-or -NHC(=O)-; or especially -OC(=O)NH- or -NH.

10

24. A compound according to claim 1, wherein W is -S-, a bond or especially -O-.

15

25. A compound according to claim 23 or 24 wherein R⁸ is optionally substituted C₀-C₃alkylcarbocycll or optionally substituted C₀-C₃-alkylheterocycll.

20

26. A compound according to claim 25, wherein the C₀-C₃ alkyl moiety is methylene or preferably a bond.

27. A compound according to claim 26 wherein R⁸ is C₀-C₃alkylaryl, or C₀-C₃alkylheteroaryl, either of which is optionally mono, di, or tri substituted with R⁹, wherein;

20 R⁹ is C₁-C₆ alkyl, C₁-C₆alkoxy, NO₂, OH, halo, trifluoromethyl, amino or amido optionally mono- or di-substituted with C₁-C₆alkyl, C₀-C₃alkylaryl, C₀-C₃alkylheteroaryl, carboxyl, aryl or heteroaryl being optionally substituted with R¹⁰; wherein

25 R¹⁰ is C₁-C₆alkyl, C₃-C₇cycloalkyl, C₁-C₆alkoxy, amino optionally mono- or di-substituted with C₁-C₆alkyl, C₁-C₃ alkyl amide, sulfonylC₁-C₃alkyl, NO₂, OH, halo, trifluoromethyl, carboxyl, or heteroaryl.

28. A compound according to claim 27 wherein R⁹ is C₁-C₆ alkyl, C₁-C₆alkoxy, amino, di-(C₁-C₃ alkyl)amino, C₁-C₃alkylamide, aryl or heteroaryl, the aryl or

30 heteroaryl being optionally substituted with R¹⁰; wherein

R^{10} is $C_1\text{-}C_6$ alkyl, $C_3\text{-}C_7$ cycloalkyl, $C_1\text{-}C_6$ alkoxy, amino, mono- or di- $C_1\text{-}C_3$ alkylamino, amido, $C_1\text{-}C_3$ alkylamide, halo, trifluoromethyl, or heteroaryl.

29. A compound according to claim 28, wherein, R^{10} is $C_1\text{-}C_6$ alkyl, $C_1\text{-}C_6$ alkoxy,

5 amino optionally mono- or di substituted with $C_1\text{-}C_3$ alkyl, amido, $C_1\text{-}C_3$ -alkylamide, halo, or heteroaryl.

30. A compound according to claim 29 wherein R^{10} is methyl, ethyl, isopropyl, tert-butyl, methoxy, chloro, amino optionally mono- or di substituted with $C_1\text{-}C_3$ alkyl,

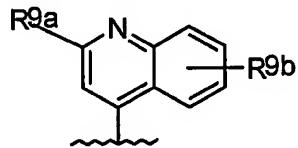
10 amido, $C_1\text{-}C_3$ alkylamide, or $C_1\text{-}C_3$ alkyl thiazolyl.

31 A compound according to claim 26, wherein R^8 is 1-naphthylmethyl, 2-naphthylmethyl, benzyl, 1-naphthyl, 2-naphthyl, or quinolinyl any of which is unsubstituted, mono, or disubstituted with R^9 as defined.

15

32 A compound according to claim 31 wherein R^8 is 1-naphthylmethyl, or quinolinyl any of which is unsubstituted, mono, or disubstituted with R^9 as defined.

33 A compound according to claim 32 wherein R^8 is:



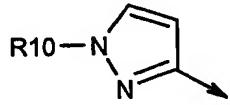
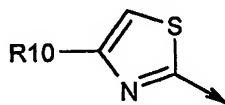
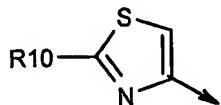
20

wherein R^{9a} is $C_1\text{-}C_6$ alkyl; $C_1\text{-}C_6$ alkoxy; thio $C_1\text{-}C_3$ alkyl; amino optionally substituted with $C_1\text{-}C_6$ alkyl; $C_0\text{-}C_3$ alkylaryl; or $C_0\text{-}C_3$ alkylheteroaryl, $C_0\text{-}C_3$ alkylheterocycl, said aryl, heteroaryl or heterocycle being optionally substituted with R^{10} wherein

25 R^{10} is $C_1\text{-}C_6$ alkyl, $C_0\text{-}C_3$ alkyl $C_3\text{-}C_7$ cycloalkyl, $C_1\text{-}C_6$ alkoxy, amino optionally mono- or di-substituted with $C_1\text{-}C_6$ alkyl, amido, $C_1\text{-}C_3$ alkyl amide; and R^{9b} is $C_1\text{-}C_6$ alkyl, $C_1\text{-}C_6$ -alkoxy, amino, di($C_1\text{-}C_3$ alkyl)amino, ($C_1\text{-}C_3$ alkyl) amide, NO_2 , OH, halo, trifluoromethyl, carboxyl.

34 A compound according to claim 33, wherein R^{9a} is aryl or heteroaryl, either of which is optionally substituted with R¹⁰ as defined.

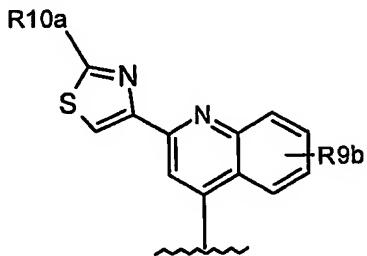
35 A compound according to 34, wherein R^{9a} is selected from the group consisted
5 of:



wherein R¹⁰ is H, C₁-C₆alkyl, or C₀-C₃alkylcycloalkyl, amino optionally mono- or di-substituted with C₁-C₆alkyl, amido, (C₁-C₃alkyl)amide.

10 36. A compound according to claim 34, wherein R^{9a} is optionally substituted phenyl, preferably phenyl substituted with C₁-C₆alkyl; C₁-C₆alkoxy; or halo.

37. A compound according to claim 33, wherein R⁸ is:



15 wherein R^{10a} is H, C₁-C₆alkyl, or C₀-C₃alkylcarbocycll, amino optionally mono- or di-substituted with C₁-C₆alkyl, amido, (C₁-C₃ alkyl)amide, heteroaryl or heterocycl; and R^{9b} is C₁-C₆ alkyl, C₁-C₆-alkoxy, amino, di(C₁-C₃ alkyl)amino, (C₁-C₃ alkyl)amide, NO₂, OH, halo, trifluoromethyl, or carboxyl.

20 38. A compound according to any claim 33, wherein R^{9b} is C₁-C₆-alkoxy, preferably methoxy.

39. A compound according to claim 1, wherein A is C(=O)NHSO₂R².

40. A compound according to claim 39, wherein R² is optionally substituted C₁-C₆ alkyl, preferably methyl.

41. A compound according to claim 39, wherein R² is optionally substituted C₃-C₇cycloalkyl, preferably cyclopropyl.

42. A compound according to claim 39, wherein R² is optionally substituted C₀-C₆alkylaryl, preferably optionally substituted phenyl.

10 43. A compound according to claim 1, wherein A is C(=O)OR¹.

44. A compound according to claim 43, wherein R¹ is H or C₁-C₆ alkyl, preferably hydrogen, methyl, ethyl, or tert-butyl.

15 45. A compound according to claim 2, wherein R⁷ is H and R⁷ is n-ethyl, cyclopropylmethyl, cyclobutylmethyl or mercaptomethyl, preferably n-propyl or 2,2-difluoroethyl.

46. A compound according to claim 2, wherein R⁷ and R^{7'} together define a spiro-cyclopropyl or spiro-cyclobutyl ring, both optionally mono or di-substituted with R^{7'a} wherein;

R^{7'a} is C₁-C₆ alkyl, C₃-C₅cycloalkyl, or C₂-C₆ alkenyl, any of which is optionally substituted with halo; or R^{7'a} is J.

20 47. A compound according to claim 47 wherein the ring is a spiro-cyclopropyl ring substituted with R^{7'a} wherein;

R^{7'a} is ethyl, vinyl, cyclopropyl, 1- or 2-bromoethyl, 1- or 2-fluoroethyl, 2-bromovinyl or 2-fluorethyl.

30 48. A compound according to claim 2, wherein R⁷ is J and R⁷ is H.

49. A compound according to claim 1, wherein J is a 3 to 8-membered saturated or unsaturated alkylene chain optionally containing one to two heteroatoms independently selected from: -O-, -S- or -NR¹²- , wherein R¹² is H, C₁-C₆ alkyl, such as methyl, or -C(=O)C₁-C₆ alkyl, such as acetyl.

5

50. A compound according to claim 49, wherein J is a 4 to 7-membered saturated or unsaturated, all carbon alkylene chain.

51. A compound according to claim 49, wherein J is saturated or mono-
10 unsaturated.

52. A compound according to claim 49, wherein J is dimensioned to provide a macrocycle of 14 or 15 ring atoms.

15 53. A pharmaceutical composition comprising a compound as defined in claim 1 and a pharmaceutically acceptable carrier therefor.

20 54. A pharmaceutical composition according to claim 53, further comprising an additional HCV antiviral, selected from nucleoside analogue polymerase inhibitors, protease inhibitors, ribavirin and interferon.

55. Use of a compound as defined in claim 1 in therapy.

25 56. Use of a compound as defined in claim 1 in the manufacture of a medicament for the prophylaxis or treatment of flavivirus infections, including HCV.

57. A method for treatment or prophylaxis of flavivirus infection such as HCV comprising the administration of an effective amount of a compound as defined in claim 1 to an individual afflicted or at risk of such infection.

30